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Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

MAILED
MAY - 9 2012

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 6,132,766 (the '766 patent) was filed on December 22, 2011, under 35 U.S.C. § 156 relating to NDA No. 22-496 for the human drug EXPAREL® (bupivacaine).

The assistance of your Office is requested in determining whether the product identified in the application, EXPAREL® (bupivacaine), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its **first** commercial marketing or use. Our analysis regarding compliance with 35 U.S.C. § 156(a)(5)(A) follows below. Additionally, we request that you confirm the approval date of October 28, 2011, so that USPTO can determine whether the application for patent term extension was filed within the sixty-day period as required by 35 U.S.C. § 156(d)(1).

Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would NOT be eligible for extension of the patent term under 35 U.S.C. § 156 as failing to comply with the requirements of 35 U.S.C. § 156(a)(5)(A).

The approved product of NDA No. 22-496 is EXPAREL®, having as the active ingredient, bupivacaine. Applicant notes that bupivacaine has not itself been previously approved. Applicant also notes that a salt of bupivacaine, bupivacaine hydrochloride, has been approved prior to the approval of EXPAREL® in the drug product Marcaine Hydrochloride.

At issue here is whether the approval of bupivacaine in EXPAREL® is the first permitted commercial marketing or use of the product as required by § 156(a)(5)(A). In order to comply with § 156(a)(5)(A), the approval of the "product" must be the first permitted commercial marketing or use. Section 156(f) defines "product" as "drug product" which in turn is defined as "the active ingredient . . . including any salt or ester of the active ingredient. . . ." Thus, the inquiry to ascertain compliance with § 156(a)(5)(A) would require determining whether the permission for the commercial marketing or use of the active ingredient, or a salt of the active ingredient or an ester of the active ingredient, was the first permitted commercial marketing or use. Here, a salt of the active ingredient, bupivacaine hydrochloride, was the first permitted

commercial marketing or use of the "product" as that term is defined in § 156(f). Thus, based on a plain reading of the statute, the approval of EXPAREL® does not comply with § 156(a)(5)(A).

In addition to the statutory analysis, the issue of compliance with 35 U.S.C. § 156(a)(5)(A) was squarely addressed by the Federal Circuit in *Photocure v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010), where the court relied on its previous decision in *Glaxo v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990) (*Glaxo II*), for its determination of eligibility of a patent for extension based on the regulatory review of Photocure's Metvixia product. Specifically, the Federal Circuit in *Photocure* stated that "[i]n *Glaxo* this court held that 'product' in §156(a) means the product that is present in the drug for which federal approval was obtained," Id. at 1376 (citing to *Glaxo II* at 894 F.2d at 393–95). Thus, *Glaxo II* is highly instructive in determining when a patent claiming an active ingredient, which may contain the same active moiety as a previously approved active ingredient, is eligible for extension.

In *Glaxo II*, the Federal Circuit affirmed the district court's determination that a patent which claimed an ester of cefuroxime was eligible for extension regardless of previous approvals of two salts of cefuroxime. *Glaxo II* at 393. Although the *Glaxo II* court did not explicitly set forth its rationale for determining that the patent was eligible for extension under section 156, in affirming the district court, the Federal Circuit implicitly adopted the district court's rationale. There, the district court in *Glaxo v. Quigg*, 706 F. Supp 1224 (E.D. Va. 1989) (*Glaxo I*) framed the rationale for eligibility as:

> the question sharply presented is whether the "product" referred to in (a)(5)(A) is cefuroxime axetil, on the one hand, or cefuroxime, the parent acid on the other. The answer to this question turns on the statutory definition of "product." Subsection (f) of Section 156 defines "product" as "a drug product," which, in turn, is defined as follows:
>
> > (2) The term "drug product" means the active ingredient of a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act) including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

35 U.S.C. § 156(f)(2).

> The central question then is whether the active ingredient of Ceftin Tablets is the ester cefuroxime axetil or the parent acid cefuroxime. If the former is true, plaintiff is entitled to an extension of its patent term. If the latter is true, then no extension would be warranted because the FDA has previously approved NDA's for Zinacef and Kefurox, two sodium salts of cefuroxime.

Glaxo I at 1227.

Additionally, the *Photocure* court pointed out that they held in *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997) that "[f]or purposes of patent term extension, this active ingredient must be present in the drug product when administered." *Photocure* at 1376.

Thus, the active ingredient of Photocure's Metvixia product is methylaminolevulinate hydrochloride, because that is the substance physically present in the final dosage form.

Applying the *Hoeschet* and *Glaxo I* analyses here, the active ingredient of EXPAREL® is bupivacaine. The question to ask is what substance is physically present in the product; here, it is bupivacaine. The next step is to ask whether bupivacaine has been previously approved. The answer to that question is no. Although bupivacaine itself has not been previously approved, a complete analysis requires to ask whether any salt or ester of bupivacaine has been previously approved by FDA. The answer to that question is yes. Because a salt of bupivacaine, bupivacaine hydrochloride, has been approved first, before the approval of EXPAREL®, the grant of permission to commercially market or use EXPAREL® is NOT the first permitted commercial marketing or use of the product/active ingredient as required by section 156(a)(5)(A) in light of the approval of Marcaine hydrochloride in 1972 (see attached information from Drugs@FDA). Accordingly, the '766 patent is ineligible for extension under the provisions of section 156.

Notwithstanding the statutory requirements, the comments of the *Photocure* court serve to buttress the conclusion that the approval of Metvixia complied with § 156(a)(5)(A), but did not provide additional criteria to confer eligibility. Applicant appears to attempt to garner support for an extension for EXAREL® by indicating that a "bupivacaine liposome injectable suspension warrants separate patenting and separate regulatory approval." Application at 4. Although the court in *Photocure* commented that Metvixia was separately patented [from Levulan] and underwent separate regulatory review [from Levulan], nothing in section 156 requires analyzing biological properties of a drug product to determine eligibility. Additionally, any "new drug," as defined in 21 U.S.C. § 321(p), must undergo separate regulatory approval as per 21 U.S.C. § 355 (no person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug). Since the additional circumstances discussed by the *Photocure* court in finding that the approval of Metvixia could support an extension of Photocure's patent are not statutory requirements, alleging similar circumstances fails to confer eligibility here.

Thus, USPTO requests that FDA consider the inquiries herein and the analysis of the issue of compliance with section 156(a)(5)(A) in reply to this letter.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Mallary K. de Merlier
Knobbe Martens, Olson & Bear, LLP
12790 El Camino Real
San Diego, CA 92130

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Drug Details

Drug Name(s)	**MARCAINE HYDROCHLORIDE (Brand Name Drug)**
FDA Application No.	**(NDA) 016964**
Active Ingredient(s)	**BUPIVACAINE HYDROCHLORIDE**
Company	**HOSPIRA**
Original Approval or Tentative Approval Date	**October 3, 1972**
Chemical Type	**1 New molecular entity (NME)**
Review Classification	**P Priority review drug**

- Therapeutic Equivalents
- Approval History, Letters, Reviews, and Related Documents
- Label Information

Products on Application (NDA) #016964
Click on a column header to re-sort the table:

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	RLD	TE Code
MARCAINE HYDROCHLORIDE	BUPIVACAINE HYDROCHLORIDE	0.25%	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE	BUPIVACAINE HYDROCHLORIDE	0.5%	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE PRESERVATIVE FREE	BUPIVACAINE HYDROCHLORIDE	0.5%	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE PRESERVATIVE FREE	BUPIVACAINE HYDROCHLORIDE	0.75%	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE PRESERVATIVE FREE	BUPIVACAINE HYDROCHLORIDE	0.25%	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE W/ EPINEPHRINE	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE	0.5%; 0.0091MG/ML	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE W/ EPINEPHRINE	BUPIVACAINE HYDROCHLORIDE;	0.25%; 0.0091MG/ML	INJECTABLE; INJECTION	Prescription	Yes	AP

	EPINEPHRINE BITARTRATE					
MARCAINE HYDROCHLORIDE W/ EPINEPHRINE PRESERVATIVE FREE	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE	0.5%; 0.0091MG/ML	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE W/ EPINEPHRINE PRESERVATIVE FREE	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE	0.75%; 0.0091MG/ML	INJECTABLE; INJECTION	Prescription	Yes	AP
MARCAINE HYDROCHLORIDE W/ EPINEPHRINE PRESERVATIVE FREE	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE	0.25%; 0.0091MG/ML	INJECTABLE; INJECTION	Prescription	Yes	AP

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